Title: Alprazolam Adverse Effect Incidence Compared to Other Benzodiazepines Within Veterans Health Administration

In 2020, alprazolam was the most prescribed benzodiazepine in the United States. Within the Veterans Affairs Healthcare System, alprazolam was the third most prescribed benzodiazepine behind clonazepam and lorazepam. Alprazolam has long been considered to have a higher risk for abuse and misuse due to the shorter half-life and street value. However, available literature does not support a clinically significant difference between benzodiazepines. This project aims to compare adverse event rates, emergency department (ED) visits and hospitalizations, as well as positive prescription drug monitoring programs (PDMP) screens for patients taking alprazolam compared to other benzodiazepines in a Veteran population.

Data will be obtained using Structured Query Language (SQL) queries from Veterans Health Administration Corporate Data Warehouse (VHA CDW), which is a copy of VHA's electronic health record. Patients who received an initial benzodiazepine prescription from one of 16 VHA health care systems from October 1, 2017 through October 1, 2022 will be eligible for inclusion. Patients with an alprazolam prescription will be compared to a cohort of patients receiving other benzodiazepine prescriptions. Exclusion criteria include less than 180 days of treatment and patients with history of seizure disorder. Descriptive statistics will be used to analyze the baseline characteristics. A multivariate model will be used to estimate the effect of benzodiazepine(s) on adverse events, hospitalizations, ED visits, and positive PDMP screens (linear regression) while controlling for confounding by individual covariates which may vary by facilities. Covariates of interest will include demographics, concomitant medications, and mental health comorbidities (a t-test will be utilized if the outcomes are continuous, and a chi-squared test will be utilized if variables are discrete). A similar analysis will be used for secondary outcomes. Discrete outcomes (e.g., yes/no adverse events, hospital admission, ED visit) will be analyzed by logistic regression models to evaluate the effect of the benzodiazepine prescription (alprazolam vs. other benzodiazepine) on the health utilization outcome while considering confounders.

Results: in progress

Conclusion: in progress

Quality Improvement Project Instructions and Template

Project Title: Alprazolam Adverse Effect Incidence Compared to Other Benzodiazepines Within Veterans Health Administration

Clinical Service: Pharmacy

Statement of the Problem

Alprazolam has long been considered a higher risk for abuse and misuse compared to other benzodiazepines due to the shorter half-life and street value in the community.[1,2] Despite long standing opinions on this medication, available literature does not support a clinically significant difference in abuse potential versus other benzodiazepines, such as diazepam, clonazepam, and lorazepam.

Evidence-Based Literature Review and Synthesis

From 1996 to 2013, the number of adult patients who received a prescription for a benzodiazepine increased from 8.1 million to 13.5 million.[3] Benzodiazepine prescriptions have tripled and the rate of benzodiazepine-related overdoses deaths have quadrupled in the same time period.[3] Moreover, from 1999 to 2017 a tenfold increase in the number of overdose deaths involving benzodiazepines was largely due to concomitant benzodiazepine and opioid therapy.[4] Compared to other commonly prescribed benzodiazepines, alprazolam is related to more emergency department (ED) visits related to drug misuse.[5] Once a patient was hospitalized, alprazolam contributed to a 1.27 times longer length of stay compared to other commonly prescribed benzodiazepines.[6] Additionally, patients taking alprazolam were 2.06 times more likely to be admitted to an intensive care unit (ICU) when compared to other benzodiazepines.[6]

Alprazolam is one of the most commonly prescribed benzodiazepines for generalized anxiety and panic disorder despite concerns of misuse liability.[2] Misuse liability is the degree to which a psychoactive drug enables misuse.[2] Alprazolam, clonazepam, and diazepam were among the top 15 drugs involved in overdose deaths in 2017.[7] However, alprazolam was the only benzodiazepine among the top ten drugs involved in overdose deaths in all United States Department of Health and Human Services (HHS) regions.[7] Alprazolam's misuse potential is due to its rapid absorption, short half-life, high potency, and more severe withdrawal symptoms.[2] When compared to diazepam, alprazolam is less lipophilic; therefore, has a smaller volume of distribution and is less protein bound. These properties contribute to alprazolam's faster metabolism and shorter duration of action.[2]

Although alprazolam's pharmacokinetic and pharmacodynamic properties suggest higher misuse potential, studies have illustrated conflicting evidence regarding its efficacy. In 1993, 84 studies were reviewed for the efficacy of alprazolam therapy when treating anxiety, panic disorder, and depression.[8] Compared to benzodiazepines (diazepam, lorazepam, and bromazepam), tricyclic antidepressants (amitriptyline, imipramine, and dothiepin), and buspirone by the Hamilton Rating Scale for Anxiety (HAM-A), alprazolam was as effective or superior. Alprazolam's onset of anxiolytic effect and anti-panic effect were quicker than other agents.[8] In 2011, a meta-analysis was conducted comparing alprazolam to other benzodiazepines and concluded no clinical difference in treatment outcomes.[9] Since the advent of newer antidepressants, such as selective serotonin reuptake inhibitors (SSRI), clinical trials involving alprazolam have significantly decreased.[2] No head-to-head trials comparing benzodiazepines to antidepressants as therapy for anxiety disorder, panic disorder, or depression exist.[2] Between alprazolam's alarming data regarding overdose and ED visits, pharmacokinetics, and conflicting efficacy data it is necessary to determine the true risk alprazolam poses to patients compared to other benzodiazepine alternatives.

Project Aims

Aim 1: Compare adverse event rates for patients taking similar lorazepam equivalents of alprazolam vs. other benzodiazepines in a Veteran population.

Aim 2: Compare rates of ED visits and hospitalizations in Veterans prescribed similar lorazepam equivalents of alprazolam vs. other benzodiazepines.

Aim 3: Compare positive PDMP screens for alprazolam vs. other benzodiazepines where there are overlapping benzodiazepine prescriptions in a Veteran population.

Project Methods

Data Collection Plan

Data from the Veterans Health Administration Corporate Data Warehouse (VHA) using SQL queries will be used to assess the multi-site variables. Patients who received a benzodiazepine prescription from one of 16 VA health care systems between October 1, 2017 and October 1, 2022 will be eligible for inclusion in the cohort study. Patients with an alprazolam prescription will be compared to the patients with other benzodiazepine prescriptions. The exclusion criteria include:

- Less than 180 days duration of treatment
- Patients with history of seizure disorder

Table 1. Baseline Characteristics

Parameters	**Definitions**
Age	• Age of patients grouped in blocks. Values are 18-40, 41-60, 61-80, 81-up, and Unknown.
Gender	• Indicates the birth sex of the patient by Male, Female, or Unknown.
Race	• Indicated by the race entered in Vista reported as Unknown, American Indian or Alaskan Native, Asian, Black or African American, Declined to Answer, Multiple, Native Hawaiian or Other Pacific Islander, or White.
Service Connection	• Ranges include Missing, SC <50%, SC > 50%, and SC=100%
Marital Status	• Indicated by status entered in CPRS reported as married or unmarried
Duration of Benzodiazepine Therapy	• Chronic usage over the last 5 years in Veteran Integrated Services Networks (VISN) 19 and 21
Anxiety and Comorbidities	
Generalized anxiety disorder, short term anxiety, anxiety associated with depression, panic disorder with or without agoraphobia	• A diagnosis is based on ICD-10 codes: o 2 documentations of it were done in the outpatient setting o 1 documentation of it was identified from an inpatient discharge diagnosis
Drug withdrawal, opioid use disorder, PTSD, depression, COPD, sleep apnea, pneumonia, overdose, fall, drug overdose, insomnia, pain, headache, substance use disorder, traumatic brain injury	• A diagnosis is based on ICD-10 codes: o 2 documentations of it were done in the outpatient setting o 1 documentation of it was identified from an inpatient discharge diagnosis
Labs	
Urine Drug Screen (UDS)	• Number of UDSs in last 12 months • Range: positive or negative for alcohol, amphetamines, opioids, and anxiolytics • Consultation with clinical subject matter experts will determine lab tests used during data pull
Medications	

The average number of anxiety medications	• Lists all active (active, hold, provider hold, suspended), recently expired (released within the past 90 days), and non-VA anxiety prescriptions for each patient • Will use drug class code to identify medications
Use of antidepressant therapy	• Lists all active (active, hold, provider hold, suspended), recently expired (released within the past 90 days), and non-VA antidepressant prescriptions for each patient • Will use drug class code to identify medications
Use of opioid therapy	• Lists all active (active, hold, provider hold, suspended), recently expired (released within the past 90 days), and non-VA opioid prescriptions for each patient • Will use drug class code to identify medications
Use of stimulant therapy	• Lists all active (active, hold, provider hold, suspended), recently expired (released within the past 90 days), and non-VA stimulant prescriptions for each patient • Will use drug class code to identify medications
Use of atypical antipsychotic therapy	• Lists all active (active, hold, provider hold, suspended), recently expired (released within the past 90 days), and non-VA atypical antipsychotics prescriptions for each patient • Will use drug class code to identify medications
Z-drugs	• Lists all active (active, hold, provider hold, suspended), recently expired (released within the past 90 days), and non-VA Z-drug prescriptions for each patient • Will use drug class code to identify medications
Healthcare Resource Utilization (HRU)	
Benzodiazepine Related Adverse Events (n,%)	• Number of adverse events for patients taking similar lorazepam equivalents of alprazolam vs. other benzodiazepines.
Benzodiazepine Related Hospitalizations (n,%)	• Number of ED visits and hospitalizations in patients taking similar lorazepam equivalents of alprazolam vs. other benzodiazepines.
Benzodiazepine Related ED Visits (n,%)	• Number of ED visits in patients taking similar lorazepam equivalents of alprazolam vs. other benzodiazepines.
PDMP Screens (n,%)	• Number of PDMP screens per patient over period of one year

Table 2. Study Outcomes Definitions

Primary Outcomes	**Definition**
Alprazolam Related Adverse Events	• Compare number of alprazolam related adverse events to number of other benzodiazepine related adverse events
Alprazolam Related Hospitalizations	• Compare rate of alprazolam related hospitalizations (number of events/100 patients) to other benzodiazepine related hospitalizations
Alprazolam Related ED Visits	• Compare rate of alprazolam related ED visits (number of events/100 patients) to other benzodiazepine related ED visits
Alprazolam Related Positive PDMP Screens	• Determine the number of PDMP screens prior to dispensing benzodiazepines, the number of annual benzodiazepine PDMP screens, and concomitant opioid prescriptions • Health Factors will be used to identify PDMPs
Secondary Outcomes	**Definition**
Benzodiazepine Related Falls (n, %)	• Will identify by the number of benzodiazepine related inpatient falls in the past 12 months using the issue brief data
Benzodiazepine Related Motor Vehicle Accidents (n, %)	• Will identify by the number of benzodiazepine related motor vehicle accidents in the past 12 months using ICD-10 code V89.2XXA
Number of Patients with Concomitant Opioid Use (n,%)	• Will identify number of patients using benzodiazepines with concomitant usage of opioids prescribed by Veterans Affairs or in the community

Descriptive Outcomes	Definition
Number of patients on alprazolam (n,%)	• Will identify the number of alprazolam prescriptions in the last 12 months
Number of patients on benzodiazepines (n,%)	• Will identify the number of other benzodiazepine prescriptions in last 12 months
Average Time to between Fills (days)	• Will be identified by the medication possession ratio
Average Change in Number of Antianxiety Medications (n)	• Will identify the number of antianxiety medications at baseline to 3-months, 6 months, 9 months, and 12-months from original benzodiazepine prescription

Analysis Plan

Descriptive statistics will be used to analyze the baseline characteristics. A multivariate model will be used to estimate the effect of benzodiazepine(s) on adverse events, hospitalizations, ED visits, and positive PDMP screens (linear regression) while controlling for confounding by individual covariates which may vary by facilities. Covariates of interest will include demographics, concomitant medications, and mental health comorbidities (T-test will be utilized if the outcomes are continuous, and Chi-square will be utilized if variables are discrete). A similar analysis will be used for secondary outcomes. Discrete outcomes (e.g., yes/no adverse events, hospital admission, ED visit) will be analyzed by logistic regression models to evaluate the effect of the benzodiazepine prescription (alprazolam vs. other benzodiazepine) on the health utilization outcome while considering confounders.

Protected Health Information

This is a retrospective review of data for a quality improvement project on patients that have already received benzodiazepine therapy. This data is already available and accessible in the medical record as part of the routine care of patients following standards of care. Data will be collected, de-identified according to HIPAA standards, aggregated, and stored on a secure server.

Assessing Risks

No physical, psychological, social, financial, privacy, confidentiality, or other reasonably foreseeable risks exist with this project.

Privacy, Data Storage & Confidentiality

Data will be collected through a query of the Veterans Integrated Service Network (VISN) 21 CDW and electronic medical record. Then, data will be de-identified, aggregated, and stored with the VA system firewall on a secure server.

Timeline

Time Completed by	Activity
October 1st	Define variables and exclusions. Submit protocol to IRB board.
October 1st-January 1st	Standardize measures; submit data request for QI project via portal. Develop SQL code to pull data related to alprazolam utilization/transition.
January 1st-April 1st	Data cleaning, revision of measures based on data availability, data merging, preliminary analysis
April 1st-June 1st	Internal review of preliminary data analysis, refinement of analysis

References

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